II. Miscellaneous

Applicants note that the only remaining rejections are those raised under 35 U.S.C. § 103. Therefore, it is assumed that all other previously raised rejections have now been withdrawn.

III. Rejection of the Claims Under 35 U.S.C. § 103

A. Rejection of Claims 1-8, 11-20, and 36-40

At paragraph 16, the Examiner maintained the rejection of claims 1-8, 11-20, and 36-40 under 35 U.S.C. § 103 as allegedly being unpatentable over Wu *et al.*, U.S. Patent No. 5,166,320 (hereinafter "Wu") or Wagner *et al., Proc. Natl. Acad. Sci. USA 87*:3410-3414 (1990) (hereinafter "Wagner") in view of Goers *et al.*, U.S. Patent No. 4,867,973 (hereinafter "Goers") or Hirsch *et al.*, U.S. Patent No. 5,428,132 (hereinafter "Hirsch"), Carriere *et al., Exp. Cell Res. 182*:114-128 (1989) (hereinafter "Carriere") and Knapp *et al., Immunology Today 10*:253-258 (1989) (hereinafter "Knapp"). Applicants respectfully traverse this rejection. Further, Applicants incorporate herein by reference, reiterate and expand upon the response filed August 26, 1996.

Specifically, at page 3, first full paragraph of the office action, the Examiner contends that:

> One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu et al. or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of nucleic acid laden conjugates to T-cells for the purpose of introducing foreign DNA into the cells for either therapeutic purposes or for the production of interleukins. One of ordinary skill in the art would have also been motivated to

> transfect T-cells through the contacting of T-cell markers with T-cell antibody specific DNA conjugates in o [sic]. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully disagree.

Applicants have previously addressed the specific issues raised by the Examiner in the responses filed March 11, 1994, November 29, 1994 and August 28, 1996. These arguments still apply and are incorporated herein by reference. Therefore, Applicants will now address the issues raised in the Examiner's "response to the traversal" at page 3, paragraph 17 of the office action. The response to the traversal is summarized at page 4 as follows:

> At issue is whether the routineer would have recognized that another "targeting" agent, such as an antibody known to be internalized into cells, would have been useful for the direction of DNA into cells and whether such a routineer would have been motivated to substitute such an antibody for the transferrin molecules of the prior art. The primary references differ from the claimed invention in only the targeting agent used to direct the DNA into a cell. One of ordinary skill in the art would have recognized that a molecule which caused internalization of a bound ligand would have been useful as a targeting component of a conjugate comprising a protein-polycation conjugate which are capable of forming soluble complexes with nucleic acids and which are also adsorbed into cells.

The Examiner draws the Applicants' attention to paragraph 1, column 2 of Wu "where it is explicitly taught that the invention is directed to the use of receptor mediated endocytosis to endow cell specificity to gene delivery." The Examiner correctly points out that the invention uses a "***ligand***-polycation-DNA complex" to achieve such delivery. However, other than a brief reference to antibodies at column 6, line 6 of Wu, the patent is almost completely drawn to the

use of the asialoglycoprotein ligand as a so-called targeting mechanism for the DNA polycation complex.

Additionally, Wu makes no specific reference to any "targeting agent" for use against cells of the T-cell lineage, as in the claimed invention. At best, there is no more than an indefinite suggestion to use ligands, e.g. antibodies, other than the asialoglycoprotein. In effect, this may disclose a potentially infinite genus of antibodies, although not the antibodies required for the claimed invention, i.e. those "capable of binding to a cell surface protein . . . expressed by cells of the T-cell lineage." Further, neither the claimed protein-polycation complex nor antibodies used in the claimed complex are *sufficiently similar* in structure to any complex or antibody specifically disclosed in Wu so as to render the claimed invention obvious. *In re Jones,* 21 U.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992).

Consistent with the above position is the more recent decision of *In re Baird,* 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994), which stated that "[a] disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a *preference* leading away from the claimed compounds." (Emphasis added). A single mention of antibodies can be said to represent a disclosure of "millions of compounds." Furthermore, Wu clearly exhibits a "preference leading away from the claimed compounds" at column 6, lines 3-5 where it recites, "*[t]ypically* glycoproteins having certain exposed terminal carbohydrate groups are used. . ." (Emphasis added). Thus, under both *Jones* and *Baird*, the claimed invention would fail to be rendered obvious in view of Wu, because Wu fails to *fairly* suggest such an invention.

As such, Wu fails to provide any suggestion for combination with the additional applied art so that such a combination would lead to a protein-polycation conjugate wherein "a protein

capable of binding to a cell surface protein by cells of the T-cell lineage, other than the transferrin receptor, so that the complexes formed are taken up into cells which express the *T cell surface protein*." (Claim 1). Therefore, there is no suggestion for combining Wu with the additional applied art.

The Examiner next states that "Wagner teache[s] the use of transferrin-polycation-DNA complexes to transfect cells, and while limited to 'transferrinfection' teaches that protein-polycation-DNA complexes were useful for delivery of DNA into cells." Applicants disagree with the broad generalization that the Examiner derives from Wagner. In particular, the Examiner's attention is drawn to Wagner at page 3414, right hand column where it is stated that "we have developed a DNA transferrinfection, in which we ***subvert*** a natural iron-uptake mechanism to transport DNA." Thus, Wagner indicates the mechanism by which he believes the DNA uptake occurs, i.e. subversion of the ***natural*** iron uptake mechanism. Clearly, such a mechanism must only apply to the use of transferrin and would not suggest a more general approach for targeting protein-polycation complexes as the Examiner contends. Nor can Wagner suggest the particular use of ligands for cell surface proteins of the T-cell lineage.

The Examiner next argues that in Goers "[t]he use of antibodies to deliver DNA and toxin into cells was well established at the time of the invention." Applicants respectfully suggest that this is irrelevant to the present issue, that is, whether there was the requisite suggestion to combine the art to arrive at the claimed invention. Merely because various antibodies were known to be internalized into a cell or that antibodies may have been used to deliver DNA, this does not mean that the requisite suggestion to combine the art as the Examiner has suggested was present

In fact, it is not even clear to Applicants where Goers describes the use of antibodies to deliver DNA to the cell. The Examiner is respectfully requested to point out such a recitation

Rather, Goers appears to relate to the use of an antibody with a therapeutic agent conjugated thereto. In any event, this still fails to provide the needed suggestion to render the claimed invention obvious.

At page 4, line 18 of the response, the Examiner alleges that "the primary reference [Wu] is different from the claimed invention in ***only*** the targeting agent used to direct the DNA into a cell." While Applicants acknowledge that this is a deficit of the primary reference, the Examiner has overlooked the additional fact that the primary reference also fails to suggest the cell type i.e., the T-cell lineage for which the claimed protein-polycation conjugates are designed. Contrary to the claimed invention, the protein-polycation complex of Wu will presumably be taken up by any cell that has a transferrin receptor, thereby not being cell-type specific. As argued above, this again is no more than at best, an indefinite suggestion to make the claimed invention because of the myriad number of possible targeting agents suggested in Wu.

The Examiner attempts to combine all the above information into a § 103 rejection alleging that one of ordinary skill in the art would recognize that molecules causing "internalization of a bound ligand would have been useful as a targeting component of a conjugate comprising a protein-polycation conjugate which are capable of forming soluble complexes with nucleic acids which are also adsorbed into the cells." Applicants maintain that this is no more than a conclusory argument and the Examiner has failed to provide the requisite suggestion to combine the applied art.

Finally, at page 4, first full paragraph of the office action, the Examiner tries to support the combination of the art based on *In re Payne* 203 U.S.P.Q. 245 (C.C.P.A. 1979). The Examiner asserts that "the court held that if two compounds are known to be analogous for a

given function, that knowledge is sufficient motivation for substituting one compound for the other." Applicants disagree with the Examiner for several reasons.

First, Applicants have been unable to find the holding asserted by the Examiner. Instead, *Payne* was directed to a finding of obviousness based upon structural similarity of a claimed compound compared to a prior art compound. As stated at 203 U.S.P.Q. 254, right-hand paragraph, the holding relates to structural obviousness in terms of the "motivation of one skilled in the art to make a claimed compound." This is clearly different than substituting "one compound for another" as the Examiner asserts. Therefore, *Payne* is clearly inapposite to the present rejection.

Second, the Examiner has not established structural similarity of the claimed conjugates to those in the prior art. Even assuming *arguendo*, that the Examiner can in fact point to the asserted holding in *Payne*, the analogy between two structurally similar chemicals and the substitution of antibodies for a ligand such as asialoglycoprotein cannot stand. The Examiner has shown no structural homology whatsoever between transferrin, asialoglycoprotein or an antibody required by the claims (directed to cell of the T-cell lineage). Merely because a particular antibody or transferrin may be internalized as an individual component, this does not indicate a structural homology between the compounds.

Third, there is not a reasonable expectation from the art that when placed into a protein-polycation complex, the individual components will necessarily have the same properties as they possessed prior to becoming part of that complex. Therefore, based on this argument, the Examiner's legal basis for substituting the anti-CD4, anti-CD7 or anti-CD5 for transferrin is inappropriate. Furthermore, based on all of the above arguments, the rejection of claims 1-8, 11-20 and 36-40 is overcome and should be withdrawn.

B. Claims 17, 20, 28-29 and 32-34

At page 4 of the Office Action, the Examiner rejected claims 17, 20, 28-29 and 32-34 under 35 U.S.C. § 103 as allegedly being "unpatentable over Wu or Wagner in view of Goers, Hirsch, Knapp and Carriere as applied above and further in view of Haseloff *et al., Nature 334:*585-591 (1988) (hereinafter Haseloff) or Rossi *et al.,* U.S. Patent No. 5,144,019 (hereinafter Rossi) and Applicants admitted prior art regarding oncogene inhibitory nucleic acids (see page 26, paragraph 3 of the specification)." Applicants respectfully traverse this rejection.

The specifics of the rejection are set forth on pages 4-5 of the office action and have already been addressed in the responses filed March 11, 1994, November 29, 1994 and August 28, 1996, all of which are incorporated herein by reference. Therefore, Applicants will only address the new issues raised in the Examiner's "response to the traversal," because Applicants previous arguments were considered but not found persuasive. The Examiner's reason for not finding the response persuasive is summarized as follows at the end of paragraph 19 of the Office Action.

> Ribozymes are a nucleic acid and one skilled in the art would have expected such ribozymes to be capable of association with the polycation-targeting agent conjugates produced in the previous rejection through the combination of references. One of ordinary skill in the art would have had a reasonable expectation of the success in forming a protein (antibody)-polycation ribozyme complex in view of the combination of references.

First, all of the arguments previously set forth to the immediately preceding rejection apply equally well to this rejection. Additionally, in the response filed August 28, 1996, Applicants attacked the use of both Haseloff and Rossi for failing to remedy the deficits of the initial combination of the art as well as for not providing either a motivation to combine the art

or a reasonable expectation of successfully obtaining the claimed invention upon combination of the art. Applicants maintain this position.

Applicants continue to assert that the use of Haseloff and Rossi is nothing more than an attempt to add individual components previously missing from the combination of the art in order to arrive at the claimed invention. As has been repeatedly argued, such picking and choosing individual components without any suggestion to do so is an improper approach to the obviousness analysis.

The Examiner has set forth no suggestion for combining the art related to ribozymes with the additional applied art. Rather, the Examiner merely refers back to the previous rejection in this office action and argues that "the obviousness of the targeting agent-polycation conjugates have been discussed above". First, this does not address the suggestion to combine applied art. The Examiner has argued the "obviousness" of the invention, and not provided a suggestion to combine the art.

Second, Applicants contend that the Examiner's argument does not provide the requisite suggestion to substitute an antibody to a T-cell protein or the use of other proteins for what had been previously used in the art. Furthermore, the Examiner's argument even fails to suggest the replacement of a specific type of nucleic acid i.e., a ribozyme for nucleic acids in general. Applicants specifically request the Examiner to indicate why a ribozyme that has a specific function is an obvious substitution for nucleic acids in general, which at best is an indefinite suggestion.

Further, the Examiner makes no more than a conclusory argument that one of skill in the art would have a reasonable expectation of success "in forming a protein (antibody)-polycation-ribozyme complex in view of the combination of references." Applicants contend that merely

referring to the combination of art as the basis for a reasonable expectation of success, does not support such an expectation. Therefore, Applicants request specific reasons why such a reasonable expectation of success exists in the applied art and further request specific citations from the art to support such an outcome.

Based on the above, Applicants have overcome the rejection of claims 17, 20, 28-29 and 32-34 under 35 U.S.C. § 103 and request its withdrawal.

C. Rejection of Claims 1 and 9-10

At page 6, paragraph 20 of the Office Action, the Examiner rejected claims 1 and 9-10 under 35 U.S.C. § 103 as being unpatentable over Wu or Wagner in view of Goers and Knapp and Carriere as applied above and further in view of Goding *et al.* Applicants respectfully traverse this rejection.

The Examiner's argument rests on the allegation that "one of ordinary skill in the art would have recognized that protein A-polycation conjugates would have been a "***universal***" reagent useful for the attachment of DNA to IgG antibodies of any specificity" (emphasis added). Applicants respectfully disagree.

The Examiner has introduced new art into the rejection that could have readily been presented before and whose introduction was *not* necessitated by amendment to the claims. The newly introduced art is Ghetie *et al, Mol. Immunol. 25:*473-477 (1988) (hereinafter Ghetie I), Ghetie *et al., Mol. Immunol. 23:*1373-1379 (1986) (hereinafter Ghetie II) andMota *et al., Mol. Immunol. 23:*1373-1379 (1986) (hereinafter Mota). Therefore, Applicants request withdrawal of the finality of the office action.

All of the newly cited art relates to protein A-ricin conjugates, not protein-polycation conjugates for the attachment of DNA to IgG antibodies. Further, at least Ghetie I and Mota relate to the binding of the protein A-ricin conjugates to "antibody coated cells." This is clearly distinct from antibody-protein A-polycation conjugates. Additionally, the reference to a "universal" reagent in Ghetie II, is to the "use of protein A-ricin toxin conjugate as a 'universal' *specific* toxin for the '*in vitro*' killing of various antibody-coated target cells," not as a (Ghetie II, last two lines of the abstract), not as a "universal reagent useful for the attachment of DNA to IgG antibodies of any specificity." (Office Action at page 7, lines 11-12).

Furthermore, in the last paragraph of Ghetie II (pg. 1378), they refer to the "universal" use of the protein A-toxin, "provided that a specific SpA reacting antitarget antibody is available." Such a requirement cannot imply use of protein A as a "universal reagent" as the Examiner asserts.

As such, the Examiner has merely stated the above, without any suggestion whatsoever from the cited art. Applicants request that the Examiner provide such evidence of a suggestion to support this rejection. Further, if additional new art is presented, Applicants request withdrawal of finality of the next office action to allow them to adequately rebut any such newly introduced art.

Additionally, the Examiner also failed to find the previous arguments persuasive for all of the "above" reasons (presumably those related to the other rejection in this office action). As such, applicants reiterate all of the arguments made to overcome the previous rejections in this office action and maintain that they apply equally well to this rejection. Therefore, for all of the above reasons, this rejection of claims 1 and 9-10 under 35 U.S.C. § 103 is overcome and should be withdrawn.

This response adds no new matter or additional claims or raises new issues. Therefore Applicants respectfully request the Examiner to consider this response after final. Further, the applicants request the reconsideration and re-examination of this application and timely allowance of the pending claims. If there are any other fees due in connection with the filing of this response other than those already submitted, please charge the fees to our deposit account 19-0036. If a fee is required for an extension of time under 37 CFR § 1.136 not accounted for above, such an extension is requested and the fee should be charged to our deposit account.

Respectfully submitted,

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